

### **REMARKS**

Claims 1, 2, 4-22 and 44-47 are pending for prosecution. Claims 1, 2, 8-11, 16-19, 22 and 44-47 have been amended. Claims 3, 12, 13 and 23-43 have been cancelled. No new matter is believed to have been added. The amendments presented herein are intended to advance prosecution to an allowance. However, Applicants reserve the right to pursue cancelled subject matter in a continuing application.

The present claimed invention requires two labels - L1 and L2. One label is attached to A-X-CH<sub>2</sub> through R<sub>3</sub>-R<sub>4</sub>-L<sub>1</sub>. The second label is attached through the R<sub>2</sub> position on either R<sub>7</sub> or R<sub>8</sub> on the purine.

The composition described in claim 1 may be used to label a protein of interest by reacting with the fused AGT moiety fused to the protein of interest (claim 44).

### **Rejection under 35 U.S.C. §102**

Claims 1-2, 4 and 6-9 have been rejected as anticipated by Zheng et al. with Calnan et al. or U.S. published application No. 2010-0105053; and Vaidyanathan et al.; and Claims 1-2, 4, 6-9 and 12 have been rejected as anticipated by Damoiseaux et al.

Each of these three references describes a benzyl guanine substrate with a single label on the benzyl group.

The Examiner asserts that the benzyl group on the guanine is R<sub>1</sub>. However, Applicants respectfully submit that this is incorrect because the benzyl group is R<sub>3</sub> not R<sub>1</sub>.

The Examiner attributes a phenylalanine anywhere in the HIV-Tat protein as representing a benzyl group for purposes of the claimed invention. The claimed substrates are not arbitrary as suggested by the Examiner.

Applicants respectfully submit that it is incorrect to recite any benzyl group from any source in any molecule as being described by Zheng et al. Zheng et al. attach a radiolabel directly to the benzyl group and fail to utilize an  $R_4$  group. When an  $R_4$  group is described, namely  $CH_2O$ , the label is a methylene.

Applicants traverse the Examiner's assertion that methylene is a spectroscopic group. However, in order to advance prosecution, "spectroscopic probe" has been substituted by "fluorophore or chromophore".

Zheng et al.

This reference describes a positron-labelled  $O^6$ -benzyl guanine (BG) analog which binds selectively to AGT for use in diagnosing, imaging and treating cancers. Figure 1 describes the chemical structure of  $O^6$ -BG analog. This structure has a core that is a purine such as shown in claim 1.

However, unlike the structures in Figure 1 of the Zheng et al. reference, present claim 1 requires that the purine core should contain a label ( $L_2$ ) and an  $R_2$  defined as a straight or branched chain alkylene group or polyvalent branched chain alkyl group with 1 to 300 carbon atoms, with optional modifications. No such substitution exists in the Zheng et al. reference. Whereas the Zheng et al. reference describes a

label on the benzene side chain (benzene -  $\text{CH}_2\text{O}^{11}\text{CH}_3$  or benzene- $^{18}\text{F}$ ), there is no suggestion or teaching of a label ( $\text{L}_2$ ) on the purine core structure in the Zheng et al. reference.

Unlike the structure in Figure 1 of the Zheng et al. reference, present claim 1 requires that one of  $\text{R}_7$  or  $\text{R}_8$  is a hydrogen while the other is not. In the purine in Figure 1 of Zheng et al., both  $\text{R}_7$  and  $\text{R}_8$  are hydrogen.

In summary, there are significant differences between the structure described in Zheng et al. and the claimed invention. This deficit is not complemented by Calnan et al. who provide an analysis of arginine rich peptides from the HIV Tat protein.

Vaidyanathan et al.

Vaidyanathan et al. describe radiolabelled benzyl guanine (purine) analogs for analyzing AGT levels in the same way as described by Zheng et al. Like Zheng et al., Vaidyanathan et al. describe a benzyl group attached via an oxygen to the purine. A label is attached directly to a carbon on this benzyl group.

The Vaidyanathan et al. reference differs from the claimed invention for reasons that include the following:

- (a) No  $\text{L}_2$  on the purine
- (b) Both  $\text{R}_7$  and  $\text{R}_8$  are protons.

Damoiseaux et al.

Damoiseaux et al. describe "the synthesis of oligonucleotides containing  $\text{o}^6$ -alkylated guanine derivatives of the type 1 and type 2" (p. 285). However, these compounds are not labelled according to

claim 1. In the Damoiseaux et al. reference, R<sub>7</sub> and R<sub>8</sub> are protons or the substrate is inserted into an oligonucleotide at R<sub>7</sub> to mimic the natural context of the modified guanine while R<sub>8</sub> is a proton. Nucleotides are not bonded to R<sub>8</sub> in nature. In Damoiseaux et al., there is no R<sub>2</sub>-L<sub>2</sub> on the purine as defined in claim 1 of the present invention.

None of the Zheng et al., Vaidyanathan et al. or Damoiseaux et al. references describe a second label as defined in claim 1 of the present invention on the purine core molecule and therefore the Examiner is respectfully requested to reverse the rejection of the claims.

#### Double Patenting Rejection

The claims in U.S. Patent No. 7,799,524 (Application serial number 10/529,651) do not describe a label (L<sub>2</sub>) on the purine. Hence, it is asserted that there is no double patenting issue. In the present claims there is L<sub>2</sub> on R<sub>7</sub> or R<sub>8</sub>. In U.S. Patent No. 7,799,524 there is a hydrogen on R<sub>7</sub> and R<sub>8</sub>.

#### 37 C.F.R. §112 rejection

Applicants have addressed Examiner's objections as follows:

1. The phrase "oligomer or short term polymers of 6-50 subunits" in claim 1 has been modified to read "oligomers of 6-50 subunits" and deleted in claim 22.
2. The phrase "a linear polymer of 6-15 subunits" has been deleted in Claims 1 and 22. The subunit of a polymer should

be understood to be a monomer which is now further defined in the claims such that "at least one subunit has an attached guanidinium group."

3. Applicants respectfully submit an error on the part of the Examiner regarding an assertion of the indefinite character of the charge on a guanidinium group. Applicants are not aware of any requirement for a balancing group to make a guanidinium neutral. For example, arginine contains a guanidinium group and no balancing group is required for arginine.
4. The claims have been amended so that L<sub>1</sub> and L<sub>2</sub> are referred to separately and in the singular.
5. The term "bridging" has been replaced by "divalent" as suggested by the Examiner.
6. The phrase "optionally containing substituents" has been removed.
7. The term "active ester" is not present in the amended claims.
8. The phrase "parts of a sequence" is replaced by "a partial amino acid sequence". This interpretation is clear from the general description in paragraph [059].
9. The word "manipulated" is deleted from Claims 44 and 47.
10. The term "O<sup>6</sup>-alkylguanine-DNA alkyltransferase" is known in the art. A skilled person in the art immediately recognizes the scope of AGT O<sup>6</sup>-alkylguanine-DNA alkyltransferases. There are numerous publications dealing with O<sup>6</sup>-alkylguanine-DNA alkyltransferases, some of which are cited in the background section. The cited publication Pegg et al., *Progress in Nucleic Acid Research and Molecular Biology* 51:167 (1995) is a standard review publication which defines the structure and function of O<sup>6</sup>-alkylguanine-DNA

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alkyltransferases. The publication is attached and should be made of record.

CONCLUSION

Applicants respectfully submit that this case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this Application is earnestly solicited.

Applicants submit a notice of appeal and petition for a three-month extension of time. Applicants authorize that the amount of \$825, covering the fees for the notice and extension, be charged to Deposit Account No. 14-0740. Please charge any deficiencies to the same Account.

Respectfully submitted,

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